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<p>(21) International Application Number: <b>PCT/US97/04537</b></p> <p>(22) International Filing Date: <b>19 March 1997 (19.03.97)</b></p> <p>(30) Priority Data: 08/659,845 7 June 1996 (07.06.96) US</p> <p>(71) Applicant: WISCONSIN ALUMNI RESEARCH FOUNDATION [US/US]; P.O. Box 7365, Madison, WI 53707-7365 (US).</p> <p>(72) Inventors: COOK, Mark, E.; 15 Kewaunee Court, Madison, WI 53705 (US). PARIZA, Michael, W.; 7102 Valhalla Trail, Madison, WI 53719 (US).</p> <p>(74) Agent: KRYSHAK, Thad; Quarles &amp; Brady, 411 East Wisconsin Avenue, Milwaukee, WI 53202-4497 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p>			
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<p>(54) Title: DIETETIC FOODS CONTAINING CONJUGATED LINOLEIC ACIDS</p>			
<p>(57) Abstract</p>			
<p>A dietetic food which contains a safe and effective amount of conjugated linoleic acid (CLA).</p>			

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## DIETETIC FOODS CONTAINING CONJUGATED LINOLEIC ACIDS

Field of the Invention

The present invention generally relates to human nutrition. More particularly, it relates to dietetic foods for animals, especially humans.

5 Background of the Invention

Dietetic foods are synthetic foods specifically formulated for people on restricted diets. Such foods, which can contain natural foods as ingredients, can take the form of either enteral compositions or parenteral compositions.

10 Enteral compositions are compositions for oral consumption or tubal feeding intended to replace natural food products that cause or aggravate allergies or other conditions in some individuals. Some common examples of enteral compositions are the baby formulae which do not contain milk proteins and  
15 margarines intended for heart patients.

Parenteral compositions are compositions for intra-venous administration to patients. Usually they are used with patients who have difficulty with orally administered food. Some common examples of parenteral compositions are solutions  
20 of electrolytes, proteins, carbohydrates and fats.

We have discovered that it is advantageous for humans to consume more conjugated linoleic acids (CLA) than are provided in dietetic foods. It is especially important that humans who are on restricted diets and consume only dietetic foods  
25 receive conjugated linoleic acid because such diets can be totally lacking in the CLA which can be found in some natural foods which are consumed in a normal unrestricted diet.

In addition to being a good calorie source in dietetic foods, CLA can be a valuable addition to dietetic foods  
30 because we have found it to be effective in increasing body protein or preventing the loss of body protein in a human, increasing food efficiency in humans, and reducing body fat. In addition, it appears to stimulate the immune system and to increase the level of CD4 and CD8 cells.

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Summary of the Invention

It is an object of the present invention to disclose dietetic foods which contain conjugated linoleic acids (CLA).

We have discovered that dietetic foods which contain a 5 safe amount of an active form of a conjugated linoleic acid (CLA), such as 9,11-octadecadienoic acid and 10,12-octadecadienoic acid, an ester thereof, a non-toxic salt thereof, and mixtures thereof, are a superior nutritional product for animals on restricted diets.

10 It will be apparent to those skilled in the art that the forementioned objects and other advantages may be achieved by the practice of the present invention.

Description of the Preferred Embodiment

The dietetic foods of the present invention contain a 15 safe and effective amount of an active form of conjugated linoleic acid (CLA) selected from a conjugated linoleic acid, such as 9,11-octadecadienoic acid and 10,12-octadecadienoic acid, an ester thereof, a non-toxic salt thereof, and mixtures thereof. These dietetic foods will also contain one or more 20 proteins, electrolytes, carbohydrates, fats, vitamins or minerals.

The amount of the CLA to be included in the dietetic food will vary with the intended use of the food and whether the dietetic food with CLA will be the sole source of nutrition. 25 However, since the CLA is a natural food ingredient and relatively non-toxic, the amount which can be consumed is not critical as long as it is enough to be effective and it is not contraindicated in the patient's diet.

30 The practice of the present invention is further illustrated by the examples which follow:

EXAMPLE 1

Synthesis of Conjugated Linoleic Acids (CLA)  
From Linoleic Acid and Safflower Oil

35 Ethylene glycol (1000 g) and 500 g potassium hydroxide (KOH) are put into a 4-neck round bottom flask (5000 ml). The flask is equipped with a mechanical stirrer, a thermometer, a

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reflux condenser, and a nitrogen inlet. (The nitrogen introduced in first run through two oxygen traps).

Nitrogen is bubbled into the ethylene glycol and KOH mixture for 20 min and the temperature is then raised to 180° C.

5 1000 g of linoleic acid, corn oil, or safflower oil then is introduced into the flask. The mixture is heated at 180° C under an inert atmosphere for 2.5 hours.

10 The reaction mixture is cooled to ambient conditions and 600 ml HCl is added to the mixture which is stirred for 15 min. The pH of the mixture is adjusted to pH 3. Next, 200 ml of water is added into the mixture and stirred for 5 min. The mixture is transferred into a 5 L separatory funnel and extracted three times with 500-ml portions of hexane.

15 The aqueous layer is drained and the combined hexane solution extracted with four 250-ml portions of 5% NaCl solution.

20 The hexane is washed three times with water. The hexane is transferred to a flask and moisture in the hexane removed with anhydrous sodium sulfate (Na<sup>2</sup> SO<sup>4</sup>). The hexane is filtered through Whatman paper into a clean 1000 ml round bottom flask and the hexane removed under vacuum with a rotoevaporator to obtain the CLA. The CLA is stored in a dark bottle under argon at -80° C until time of use.

25 This method can be modified so as to utilize only food-grade reagents and solvents as listed in *Food Chemicals Codex*, third edition, National Academy Press, 1981.

The active forms of CLA include, in addition to the free acids, the non-toxic salts thereof, the active esters thereof, such as triglycerides, and mixtures thereof.

30 The free conjugated linoleic acids (CLA) have been previously isolated from fried meats and described as anticarcinogens by Y. L. Ha, N. K. Grimm and M. W. Pariza, in *Carcinogenesis*, Vol. 8, No. 12, pp. 1881-1887 (1987). Since then, they have been found in some processed cheese products.

35 Y. L. Ha, N. K. Grimm and M. W. Pariza, in *J. Agric. Food Chem.*, Vol. 37, No. 1, pp. 75-81 (1987). The free acid forms of the CLA may be prepared by isomerizing linoleic acid. The terms "conjugated linoleic acids" and "CLA" as used herein are

intended to include 9,11-octadecadienoic acid, 10,12-octadecadienoic acid; non-toxic salts thereof; esters thereof; and mixtures thereof. The non-toxic salts of the free acids may be made by reacting the free acids with a non-toxic base.

5 One method of synthesizing CLA is described in Example 1. However, CLA may also be prepared from linoleic acid by action of a linoleic acid isomerase from a harmless microorganism, such as the Rumen bacterium Butyrivibrio fibrisolvens.  
10 Harmless microorganisms in the intestinal tracts of rats and other monogastric animals may also convert linoleic acid to CLA (S. F. Chin, J. M. Storkson, W. Liu, K. Allbright and M. W. Pariza, 1994, *J. Nutr.* 124; 694-701.

15 The CLA obtained by the practice of the described methods of preparation contains one or more of the 9,11-octadecadienoic acids and/or 10,12-octadecadienoic acids and active isomers thereof. It may be free or bound chemically through ester linkages. The CLA is heat stable and can be used as is, or dried and powdered. The CLA is readily converted into a non-toxic salt, such as the sodium or potassium salt, by reacting chemically equivalent amounts of the free acid with an alkali hydroxide at a pH of about 8 to 9. CLA also can be esterified to glycerol to form mono-, di-, and triglycerides.

20 Theoretically, 8 possible geometric isomers of 9,11- and 10,12-octadecadienoic acid (c9, c11; c9,t11; t9,c11; t9,2t11; c10,c12; c10,t12; t10,c12 and t10,t12) would form from the isomerization of c9,c12-octadecadienoic acid. As a result of the isomerization, only four isomers (c9,c11; c9,t11; t10,c12; and c10,c12) would be expected. However, of the four isomers, 25 c9,t11- and t10,c12- isomers are predominantly produced during the autoxidation or alkali-isomerization of c9,c12-linoleic acid due to the co-planar characteristics of 5 carbon atoms around a conjugated double-bond and spatial conflict of the resonance radical. The remaining two c,c-isomers are minor contributors.

30 The relatively higher distribution of the t,t-isomers of 9,11- or 10,12-octadecadienoic acid apparently results from the further stabilization of c9,t11- or t10,c12- geometric

isomers, which is thermodynamically preferred, during an extended processing time or long aging period. Additionally the t,t-isomer of 9,11- or 10,12-octadecadienoic acid that was predominantly formed during isomerization of linoleic acid 5 geometrical isomers (t9,t12-, c9,t12- and t9,c12-octadecadienoic acid) may influence the final ratio of the isomers or the final CLA content in the samples.

Linoleic acid geometrical isomers also influence the distribution of minor contributors (c,c-isomers of 9,11- and 10,12-, t9,c11- and c11,t12-octadecadienoic acids). The 11,13-isomer might be produced as a minor product from c9,c12-octadecadienoic acid or from its isomeric forms during processing.

The exact amount of CLA to be incorporated into a 15 dietetic food, of course, depends upon the intended use of the food, the form of CLA employed, and route of administration. It also can depend upon the isomer ratios. However, generally the dietetic food will contain the equivalent of about 0.5 g to about 1.0% g of CLA by weight of the dietetic food. The 20 CLA content also can be expressed as the amount of CLA based on the total calories in the serving e.g. 0.03 to 3 gram CLA per 100 calorie serving. Alternatively, the amount of CLA can be expressed as a percentage of the lipid or fat in the food, such as 0.3% to 100% of the food lipid, or as an amount of CLA 25 per gram of food lipid, such as 3 to 1000 mg CLA per gram of lipid.

When the patient's sole source of food is the dietetic food, the amount of CLA employed should be such that the patient consuming the dietetic food will obtain from about 500 30 parts per million (ppm) to about 10,000 ppm of CLA in his diet. If the dietetic food is not the sole source of food higher or lower amounts of the dietetic food might need to be consumed to reach these levels. However, the upper limit of the amount to be employed is not critical because CLA is 35 relatively non-toxic and it is a normal constituent of the human diet (including human breast milk).

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The CLA to be incorporated into the dietetic food can be in the form of the free acid, a salt thereof; an ester thereof, such as a triglyceride; and any mixtures thereof.

Example 1

5       A liquid dietetic food for parenteral administration to humans contains emulsified fat particles of about 0.33-0.5  $\mu\text{m}$  in diameter. In addition, the emulsions can contain Water for Injection USP as a diluent, egg phosphatides (1-2%) as an emulsifying agent and glycerin (2-3%) to adjust toxicity.

10      These emulsions can be infused intravenously to patients requiring parenteral nutrition. Representative formulae of the present invention would contain the same ingredients plus 0.5 mg/gm to 10 mg/gm of CLA or alternatively, 0.3% to 100% CLA based on the food lipid or 0.03 gram to .3 gram per 100 calorie serving. For such parenteral foods the CLA usually should be present in the form of the triglycerides.

Example 2

20      A milk protein-free, soy protein-based, baby formula is prepared which contains CLA. Such a baby formula will contain about 0.5 mg/gram to about 10 mg/gram of CLA or about 0.03 gram to 0.5 gram CLA per 100 calorie serving or 0.3% to 100% CLA based on the lipid in formula.

One serving (100 calories) of a representative formula can contain the following:

25	Protein	2.66 g
	Fat	5.46 g
	Carbohydrate	10.1 g
	Water	133 g
	CLA	0.3 g
30	Vitamins and Minerals	(RDA amounts)

Example 3

A dietetic margarine of the present invention for use in a heart-healthy diet is a semi-solid or solid vegetable oil-based margarine which, in addition to the usual ingredients, 35 contains CLA. Such a margarine will contain about 0.25

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mg/gram to about 10 mg/gm of CLA or about 0.03 gram to 0.5 gm CLA per 100 calorie serving.

Example 4

5 A low residue liquid enteral dietetic product useful as a high-protein, vitamin and mineral supplement contains added CLA. The amount of CLA present can be about 0.05% to about 5% by weight of CLA or about 0.3% to about 100% of the lipid present or about 0.03 to 0.3 gram CLA per 100 calories.

10 One serving (140 calories) of a representative formula can contain the following:

	Protein (egg white solids)	7.5 g
	Fat (CLA)	0.1 g
	Carbohydrate (sucrose, hydrolyzed corn starch)	27.3g
15	Water	1.9 g
	Vitamins and Minerals	(RDA amounts)

It will be readily apparent to those skilled in the art that many dietetic foods, including those described in U.S. Patent Nos. 4,282,265 and 5,470,839, can be improved by adding 20 CLA to the food or by replacing some of the fat in the food with CLA.

It also will be readily apparent to those skilled in the art that a number of modifications or changes may be made without departing from the spirit and scope of the present 25 invention. Therefore, the invention is only to be limited by the claims.

CLAIMS

1. A dietetic food containing a member selected from the class consisting of a conjugated linoleic acid, an ester thereof, a non-toxic salt thereof, and mixtures thereof; said member being present in amount of at least 3 mg per gram of 5 lipid in the food.
2. A dietetic food of claim 1 in which the dietetic food is a baby formula.
3. A dietetic food of claim 1 in which the dietetic food is suitable for enteral administration.
- 10 4. A dietetic food of claim 1 in which the member is present as an ester and dietetic food is suitable for parenteral administration.
- 15 5. In a dietetic food, the improvement which comprises incorporating in said food a safe amount of a member selected from the class consisting of a conjugated linoleic acid, a salt thereof, an ester thereof, and mixtures thereof.
6. A dietetic food of claim 5 in which the amount of the member is equivalent to at least about 3.0 mg per gram of product lipid of the dietetic food.
- 20 7. A method of modifying a synthetic formulated dietetic food which comprises incorporating in said food at least about 3.0 mg per gram of CLA per gram of product lipid.
- 25 8. A dietetic food adapted for infant feeding as the sole item of diet, said food comprising assimilable carbohydrate, protein and fat, wherein the fat comprises at least about 3.0 mg of CLA per gram of fat.

# INTERNATIONAL SEARCH REPORT

Inte	Application No
PCT/US 97/04537	

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 A23L1/30 A23D7/00 //A23C9/152

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 A23L A23D A23C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DMZ LEBENSMITTELINDUSTRIE UND    MILCHWIRTSCHAFT,    vol. 116, no. 26, December 1995,    pages 1268-1272, XP002035276    KAMMERLEHNER: "Linolsäure und konjugierte    Linolsäuren - ihr Vorkommen im Milchfett,    ihre biologische Bedeutung"    see page 1270 - page 1271; tables 1,2    ---    -/-</p>	1,3,5

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF FOOD COMPOSITION AND ANALYSIS, vol. 5, 1 January 1992, pages 185-197, XP000575131 CHIN S F ET AL: "DIETARY SOURCES OF CONJUGATED DIENOIC ISOMERS OF LINOLEIC ACID, A NEWLY RECOGNIZED CLASS OF ANTICARCINOGENS" see the whole document	1-3,8
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A	---	4
X	FOOD CHEM., vol. 47, no. 3, 1993, pages 257-261, XP002035277 SANTHA ET AL.: "Conjugated linoleic acid concentrations in processed cheese containing hydrogen donors, iron and dairy-based additives" see the whole document	1,3
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X	US 5 428 072 A (COOK) 27 January 1995 see the whole document	1,5-7
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Y	see page 266 - page 268	5
X	---	
X	NUTRITION REPORTS INTERNATIONAL, vol. 38, no. 5, November 1988, pages 937-944, XP000607841 FOGERTY A C ET AL: "OCTADECA-9,11-DIENOIC ACID IN FOODSTUFFS AND IN THE LOPIDS OF HUMAN BLOOD AND BREAST MILK" see tables I,II	1,3-5
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**INTERNATIONAL SEARCH REPORT**

Int'l Application No  
PCT/US 97/04537

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIPID TECHNOL., vol. 7, no. 6, 1995, pages 133-135, XP000677845 GURR: "A trans fatty acid that is good to eat ? conjugated linoleic acid" see page 134 left column and right column last paragraph ---	1-3,8
X	NATURE, vol. 352, 22 August 1991, page 673 XP002035278 SARKAR : "Beneficial ghee ?" see the whole document ---	1
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Y	US 5 068 119 A (KLEMMAN) 26 November 1991 see column 6 lines 28-38, 44-68 see column 7, line 1 - line 5 see examples 8,9 ---	1,3-7
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/04537

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